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Sertifikaat

REPUBLIEK VAN SUID-AFRIKA

Certificate

PATENTKANTOOR 10/009214

PATENT OFFICE

DEPARTEMENT VAN HANDEL EN NYWERHEID

REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF TRADE AND INDUSTRY

Hiermee word gesertifiseer dat
This is to certify that

4

the documents annexed hereto are true copies of:

Application forms P.1 and P.3, provisional specification and drawings of South African Patent Application No. 2000/1247 as originally filed in the Republic of South Africa on 10 March 2000 in the name of TECHNOLOGY FINANCE CORPORATION (PROPRIETARY) LIMITED for an invention entitled: "AN IMPLANT".

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

PRETORIA in die Republiek van Suid-Afrika, hierdie 16 dag van May 2001
in the Republic of South Africa, this day of

Registrateur van Patente
Registrar of Patents

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978
APPLICATION FOR A PATENT AND
ACKNOWLEDGEMENT OF RECEIPT
(Section 30(1) Regulation 22)

REPUBLIC OF SOUTH AFRICA REVENUE
FORM P.1
(to be lodged in duplicate)
10.3.00 R 060.00

THE GRANT OF A PATENT IS HEREBY REQUESTED BY THE UNDERMENTIONED APPLICANT ON THE BASIS OF THE PRESENT APPLICATION FILED IN DUPLICATE
REPUBLIEK VAN SUID AFRIKA

21	01	PATENT APPLICATION NO 20001247

IMASS 370
A&A REF V13894

71	FULL NAME(S) OF APPLICANT(S)

TECHNOLOGY FINANCE CORPORATION (PROPRIETARY) LIMITED

ADDRESS(ES) OF APPLICANT(S)

Ground Floor, Corporate Place, 23 Fredman Avenue, Sandton, Republic of South Africa

54	TITLE OF INVENTION

AN IMPLANT

Only the items marked with an "X" in the blocks below are applicable.

[ ] THE APPLICANT CLAIMS PRIORITY AS SET OUT ON THE ACCOMPANYING FORM P.2. The earliest priority claimed is

Country: No: Date:

[ ] THE APPLICATION IS FOR A PATENT OF ADDITION TO PATENT APPLICATION NO 21 01

[ ] THIS APPLICATION IS A FRESH APPLICATION IN TERMS OF SECTION 37 AND BASED ON APPLICATION NO 21 01

THIS APPLICATION IS ACCOMPANIED BY:

[X] A single copy of a provisional specification of 12 pages
[X] Drawings of 1 sheets
[ ] Publication particulars and abstract (Form P.8 in duplicate) (for complete only)
[ ] A copy of Figure of the drawings (if any) for the abstract (for complete only)
[ ] An assignment of invention
[ ] Certified priority document(s). (State quantity)
[ ] Translation of the priority document(s)
[ ] An assignment of priority rights
[ ] A copy of Form P.2 and the specification of RSA Patent Application No 21 01
[X] Form P.2 in duplicate
[ ] A declaration and power of attorney on Form P.3
[ ] Request for ante-dating on Form P.4
[ ] Request for classification on Form P.9
[ ] Request for delay of acceptance on Form P.4
[ ] Extra copy of informal drawings (for complete only)

74	ADDRESS FOR SERVICE: Adams & Adams, Pretoria

Dated this **10** day of **March 2000**

ADAMS & ADAMS
APPLICANTS PATENT ATTORNEYS

The duplicate will be returned to the applicant's address for service as proof of lodging but is not valid unless endorsed with official stamp

OFFICIAL DATE STAMP
REGISTRAR OF PATENTS, DESIGNS, TRADE MARKS AND COPYRIGHT
2000 -03- 10
REGISTRATEUR VAN PATENTE, MODELLE, HANDELSMERKE EN OUTEURSREG
REGISTRAR OF PATENTS

A&A P201

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PRETORIA

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978
DECLARATION AND POWER OF ATTORNEY
(Section 30 - Regulation 8, 22(i)(c) and 33)

FORM P.3

PATENT APPLICATION NO	
21	01

A&A Ref: V13894 GSK

LODGING DATE	
22	10 MARCH 2000

FULL NAME(S) OF APPLICANT(S)	
71	TECHNOLOGY FINANCE CORPORATION (PROPRIETARY) LIMITED

FULL NAME(S) OF INVENTOR(S)	
72	RICHTER, Paul Wilhelm THOMAS, Michael Edward

EARLIEST PRIORITY CLAIMED	COUNTRY		NUMBER		DATE
	33	--	31		

NOTE: The country must be indicated by its International Abbreviation - see schedule 4 of the Regulations

REGISTRAR OF PATENTS, DESIGNS, TRADE MARKS AND COPYRIGHT
2000 -06- 02
REGISTRATEUR VAN PATENTE, MODELLE, HANDELSMERKE EN OUTEURSREG

TITLE OF INVENTION	
54	"AN IMPLANT"

* I/We DR O SAFRIEL

hereby declare that :-

~~1. I/we am/are the applicant(s) mentioned above;~~

** 2. I/we have been authorized by the applicant(s) to make this declaration and have knowledge of the facts herein stated in the capacity of ACTING MANAGING DIRECTOR of the applicant(s);

*** 3. the inventor(s) of the abovementioned invention is/are the person(s) named above and the applicant(s) has/have acquired the right to apply by virtue of an assignment from CSIR in whom the invention vests in terms of section 13 or 14 of act 82 of 1984 or section 13 of act 46 of 1988;

4. to the best of my/our knowledge and belief, if a patent is granted on the application, there will be no lawful ground for the revocation of the patent;

**** ~~5. this is a convention application and the earliest application from which priority is claimed as set out above is the first application in a convention country in respect of the invention claimed in any of the claims;~~ and

6. the partners and qualified staff of the firm of **ADAMS & ADAMS**, patent attorneys, are authorised, jointly and severally, with powers of substitution and revocation, to represent the applicant(s) in this application and to be the address for service of the applicant(s) while the application is pending and after a patent has been granted on the application.

SIGNED THIS 23 DAY OF MAY 2000

X Dr O Sahriel

Company Name: TECHNOLOGY FINANCE CORPORATION (PROPRIETARY) LIMITED
Full Names: DR O SAFRIEL
Capacity: ACTING MANAGING DIRECTOR

(no legalization necessary)

* In the case of application in the name of a company, partnership or firm, give full names of signatory/signatories, delete paragraph 1, and enter capacity of each signatory in paragraph 2.
** If the applicant is a natural person, delete paragraph 2.
*** If the right to apply is not by virtue of an assignment from the inventor(s), delete "an assignment from the inventor(s)" and give details of acquisition of right.
**** For non-convention applications, delete paragraph 5.

A & A Ref No: V13894

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PATENT ATTORNEYS
PRETORIA

FORM P6

REPUBLIC OF SOUTH AFRICA
Patents Act, 1978

PROVISIONAL SPECIFICATION

(Section 30 (1) - Regulation 27)

21	01	OFFICIAL APPLICATION NO

20001247

22	LODGING DATE

10 March 2000

71	FULL NAME(S) OF APPLICANT(S)

TECHNOLOGY FINANCE CORPORATION (PROPRIETARY) LIMITED

72	FULL NAME(S) OF INVENTOR(S)

RICHTER, Paul Wilhelm
THOMAS, Michael Edward

54	TITLE OF INVENTION

AN IMPLANT

THIS INVENTION relates to an implant. It relates also to a method of making an implant.

According to a first aspect of the invention, there is provided an implant, which includes a body of hydroxyapatite with zones of tricalcium phosphate located in the hydroxyapatite body, and with the sizes of the major proportion of the zones of tricalcium phosphate being from 10 to 500 microns.

By 'size' is meant the effective cross-sectional dimension of a zone of tricalcium phosphate. When the zones are spherical, their size is thus their diameter; however, when the zones are non-circular, their size is the same as the mesh size through which such zones of tricalcium phosphate will pass.

The hydroxyapatite of the body is in dense and crystalline form, and is thus substantially non-resorbable in use. The tricalcium phosphate is also in crystalline form, and may be in either the α or the ß form, both of which are resorbable in use. However, the ß or high temperature form is preferred.

The zones of tricalcium phosphate may all be of substantially the same size, and may be randomly dispersed throughout the hydroxyapatite body. Some of the zones may thus be located at the surface of the body. The size of the zones may, in particular, be from 10 to 300 microns.

The proportion of hydroxyapatite to tricalcium phosphate in the implant may be from 4:1 to 3:2, on a mass basis, preferably about 2:1.

Macropores or macroporous spaces may be provided in the body. The macropores may be substantially spherical, and at least some may be interconnected. In particular, the macropores that are interconnected may be of spherical, intercoalesced form, ie adjacent macropores are coalesced together and are thus not interconnected by elongate passageways. The macropores may be from 100 to 2000 microns in size, ie may have diameters of 100 to 2000 microns, preferably 400 to 800 microns.

All, or the majority of, the macropores may be of substantially the same size. The macropores may occupy from 20% to 80% of the total volume of the body. For example, the macropores may occupy about 60% of the total volume of the body. The macropores may be randomly interspersed throughout the body. Thus, the body may have a network of interconnected coalesced rounded inner macroporous spaces.

The body may also, if desired, be provided with surface concavities which may have diameters of from 100 to 2000 microns, preferably 400 to 800 microns, and depths of 500 to 1000 microns, preferably 200 to 400 microns. The surface concavities may be hemispherical. The surface concavities may be interconnected with the macropores by being coalesced therewith.

If desired, micropores may also be provided in the body. While some of the micropores may also be substantially spherical, the majority of the micropores will be of irregular shape. The micropores may also be randomly interspersed throughout the body. The micropores may be separate from one another, ie not connected together. The micropores may all be of substantially the same size, and may be smaller than 50 microns, ie have diameters smaller than 50 microns, preferably smaller than 10 microns. The micropores, when present, may occupy 60% or less of the total volume of the body, excluding the volume occupied by the macropores, ie the residual volume of the body after the volume of the macropores has been excluded. Typically, the micropores may occupy about 40% of the residual body volume.

The implant is suitable for implanting into a subject. It can thus be used either as a bone implant at a site where bone growth is required, or as an implant in a site where only soft tissue is in direct contact with the implant without any bone present in the immediate vicinity of the implant ie a soft tissue implant.

The hydroxyapatite and tricalcium phosphate are sintered bioactive ceramic biomaterials, and the implant has both intrinsic osteoconductivity, ie permitting bone growth into its pores or porous spaces when it is in direct contact with viable bone, and intrinsic osteoinductivity, ie permitting bone growth into its pores independently of the presence of viable bone in contact with the implant.

According to a second aspect of the invention, there is provided a method of making an implant, which method includes

mixing hydroxyapatite powder with a thermoplastic binder at elevated temperature, to produce a first powder/binder mixture;

comminuting the first powder/binder mixture to obtain a first granular mixture having granules or particles with sizes from 10 to 500 microns;

mixing tricalcium phosphate powder with a thermoplastic binder at elevated temperature, to produce a second powder/binder mixture;

comminuting the second powder/binder mixture to obtain a second granular mixture having granules or particles with sizes from 10 to 500 microns;

combining the first and second granular mixtures to form a combined mixture;

optionally, mixing the combined mixture with fugitive phase particles which are heat decomposable, with the fugitive phase particles having sizes of 100 to 2000 microns;

pressing or compacting the resultant mixture into a green compact or body;

when the fugitive phase particles are present, heating the green compacts or bodies to above the decomposition temperature of the fugitive phase particles; and

sintering the resultant green body, to obtain an implant.

Any suitable thermoplastic binder, such as a commercial polymeric binder used for extrusion or injection moulding of ceramic materials, may be used, provided it allows ambient temperature compaction of the granules to a strength adequate for further processing. The same thermoplastic binder may be used for the first and second powder/binder mixtures.

The temperature at which the mixing of the hydroxyapatite powder and the tricalcium phosphate powder with the thermoplastic binder to produce the first and second powder/binder mixtures takes place depends on the thermoplastic binder used, but is typically around 120°C.

The comminution of the first and second powder/binder mixtures may be effected by crushing the mixtures, and sieving them to the required granule or particle size.

In forming the combined mixture, the first and second mixtures are used in a desired mass ratio, depending on the desired relative portions of hydroxyapatite and tricalcium phosphate in the implant. The mixing may be effected by homogenizing the combined mixture in a ball mill without milling media, for an extended period of time, eg for a period of several hours.

The fugitive phase particles may be stearic acid particles, which may be substantially spherical. The stearic acid particles will be selected such that they provide macropores or macroporous spaces of a desired size in the implant. Thus, typically, stearic acid particles having a size range of 500 to 1000 microns are used.

The combined mixture is admixed with the fugitive phase particles in a desired mass ratio in order to provide a resultant implant having a desired macropore volume. Thus, if a desired macropore volume of approximately 60% of the total implant volume is desired, then the mass proportion of combined mixture to fugitive phase particles will be about 1,27:1 by mass.

To form the green compact or body, the mixture may be pressed or compacted at a pressure of about 20MPa and machined, if necessary.

The temperature to which the green compacts or bodies are heated is dependent on the fugitive phase used. However, when stearic acid particles are used as the fugitive phase, the green compacts are typically heated to about 500°c, to allow melting and decomposition of the stearic acid, thereby forming in the green compacts or bodies, interconnected macropores produced by the decomposition of the stearic acid particles. The sintering is thus effected at elevated temperature, ie at a temperature above 500°C. The sintering temperature and time is set or limited by the level of micropores required in the resultant implant. For

example, to obtain a microporosity level or volume of 40% of the residual solid component of the implant, sintering may be effected at about 1100°C for one hour.

The invention will now be described in more detail, with reference to the accompanying drawing which show a cross-sectional view of an implant according to the first aspect of the invention.

In the drawing, reference numeral 10 generally indicates an implant according to the invention. The implant is shown as being circular in cross-section. This is for ease of illustration; in practice the implant shape and size will be dictated by its desired end use.

The implant 10 includes a body 12 of hydroxyapatite. Zones 14 of ß-tricalcium phosphate are randomly dispersed throughout the body 12. The zones 14 are of approximately the same size, and have a size of about 300 microns.

The mass ratio of hydroxyapatite to ß-tricalcium phosphate in the body 10 is approximately 2:1.

The body 10 also includes a plurality of randomly interspersed spherical macropores, each generally indicated by reference numeral 16. Some adjacent macropores 16 are coalesced together so that the adjacent macropores 16 are connected together by means of a connecting line 18 rather than by means of elongate

tunnels or passageways. The macropores 16 are all of approximately the same size, and they have diameters in the range of 400 to 800 microns. The macropores 16 occupy about 60% of the total volume of the body 10.

The body 10 is also provided with randomly dispersed micropores 20 having a size smaller than 10 microns. While the micropores are shown as being spherical, in practice only some of the micropores will in fact be spherical; the majority thereof will be of irregular shape. The individual micropores 20 are not connected together. The micropores 20 are dispersed throughout the body 10 as well as throughout the zones 14. The micropores 20 occupy about 40% of the residual volume of the body 12, ie the volume of the body 12 remaining after the combined volume of all the macropores 16 have been deducted from the initial volume of the body 12.

The implant 10 is formed by compounding hydroxyapatite powder with a commercial thermoplastic polymeric binder at a temperature of about 120°C to produce a first powder/polymer mixture. This mixture is crushed and sieved to a particle size smaller than 300 microns. In this fashion, a first granular mixture is obtained.

ß-tricalcium phosphate powder is similarly compounded with the same thermoplastic polymeric binder at an elevated temperature of about 120°C, to produce a second powder/polymer mixture. This mixture is also crushed and sieved to a particle size smaller than 300 microns, to obtain a second granular mixture.

Any commercial thermoplastic polymeric binder suitable for extrusion or injection moulding of ceramic materials, may be used, provided it allows ambient temperature compaction of the granules of the mixtures to a strength adequate for further processing.

The first granular mixture is combined with the second granular mixture in a 2:1 ratio by mass, and homogenized by rolling thereof in a ball mill without milling media, for an extended period of several hours.

The resultant powder is mixed with substantially spherical particles of stearic acid which have been sieved to a size range of 500 to 1000 microns, with the mass proportion of powder to fugitive phase particles being 1,27:1. The resultant mixture is pressed or compacted at a pressure of 20MPa, and machined if necessary. In this fashion, green compacts are obtained.

The green compacts are heated to 500°C, to allow melting and decomposition of the stearic acid particles, resulting in unsintered green compacts having interconnected coalesced macropores therein achieved by decomposition of the stearic acid particles.

The temperature is then further increased to achieve sintering of the hydroxyapatite and ß-tricalcium phosphate powders. Micropores form in the body. The desired degree of microporosity is controlled by limiting the maximum conditions for sintering.

For example, to achieve a microporosity level of 40% of the residual volume of the body, ie after the volume occupied by the macropores has been deducted from the initial volume of the implant body, to below 1100°C for one hour.

The resultant implant has a final macroporous volume of approximately 60%, based on the total volume of the implant. The implant is suitable for use as a bone implant or as a soft tissue implant. When used as a bone implant, it has both osteoconductivity and osteoinductivity properties.

When used as either a bone implant or a soft tissue implant, the hydroxyapatite body 12 is non-resorbable since it is in dense crystalline form. However, the ß-tricalcium phosphate zones 14 are resorbable. Thus, the implant 10 has high bioactivity with partial controllable resorbability. Over time, all these zones 14 will resorb, leaving a skeleton or scaffold of hydroxyapatite, where bone growth can take place.

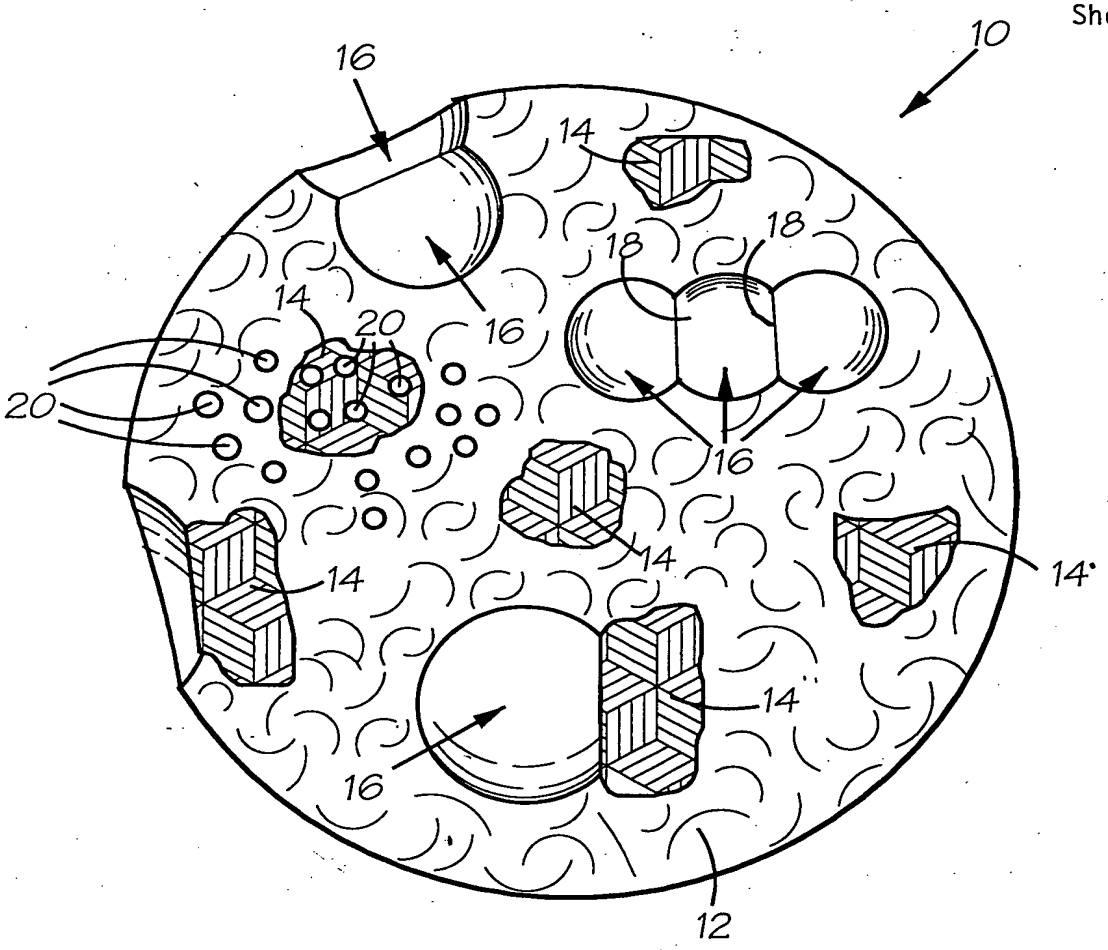
It is believed that, with the zones 14 which are larger than 10 microns, faster resorption of the tricalcium phosphate in these areas will take place than would be obtained with a finer distribution of tricalcium phosphate, eg single tricalcium phosphate particles in a mixture of such particles and hydroxyapatite particles. Penetration of hard or soft tissue then takes place into the ceramic structure at the locations where resorption of the tricalcium phosphate has occurred. This

occurs while the basic ceramic hydroxyapatite scaffold is preserved.

DATED THIS 10TH DAY OF MARCH 2000

ADAMS & ADAMS
APPLICANTS PATENT ATTORNEYS

TECHNOLOGY FINANCE CORPORATION (PROPRIETARY) LIMITED



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